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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,909	10/01/2003	Harald Kropshofer	21388	8340

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,909	KROPSHOFER ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-33* is/are pending in the application.

4a) Of the above claim(s) *28-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/20/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to comply with the sequence rules.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/18/09 has been entered.

Applicant's amendment filed 9/8/09 is acknowledged and has been entered.

Note that the Examiner of your application in the PTO has changed.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. For example, SEQ ID NO are required for sequences appearing at [0124], [0131], and Figures 1 and 2.

Applicant is advised that for any response to be considered fully responsive said response has to be fully responsive to the sequence compliance requirements.

3. The use of the trademarks SEPHAROSE, ZWITTERGENT, PARTISPHERE and ULTRAFLEX have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

6. The disclosure is objected to because of the following informality: Applicant is required to disclose the complete address of ATCC, *i.e.*, American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

Appropriate correction is required.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 6 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the disclosure as originally filed is as follows: "using 0.1% diluted acid...diluted acetonitrile (0.1%), diluted acetic acid (0.1%)".

Applicant points (in Applicant's response filed 1/17/08 on page 9) to support for the said amendatory material at [0041] and [0106] of the specification. However, the disclosure at [0041] is to "using diluted acid, e.g., diluted acetonitrile...diluted acetic acid and heating...or dilute trifluoro acetic acid at 37" degrees C. The said disclosure does not provide the percent of the acid. The disclosure at [0106] is to using 0.1% trifluoracetic acid in water to elute the bound peptides from the MHC binding groove. There is no disclosure of percent acid for acetonitrile or acetic acid, nor is there disclosure for the genus of "using 0.1% diluted acid", just for the species of using 0.1% trifluoracetic acid.

10. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolating MHC antigenic peptides in the recited amounts from cells or tissues that express MHC or comprise cells that express MHC, including whole blood, does not reasonably provide enablement for isolating MHC antigenic peptides in the recited amounts from any body fluid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass isolating MHC antigenic peptides from any body fluid of a mammalian organism, such as for example, urine, plasma, tears, saliva, in which instance MHC may not be present because the body fluid does not comprise shed MHC or cells that express MHC, or NHC complexes may not be present in the recited amount, or may not comprise intact complexes with bound peptides.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method can be used.
The specification discloses no working examples with regards to isolation of antigenic peptides from any such body fluid except from whole blood (*i.e.*, from dendritic cells present in whole blood).

The specification at [0029] discloses that each single peptide whose sequence has to be determined is represented in only femtomolar amounts 1 ug MHC class II (16 pmol) may carry dominant peptide species, with each single peptide attaining an occupancy of 0.1-2% which equals about 16-320 femtomoles. The specification continues "The methods of the present invention allow the isolation of these femtomolar amounts of antigenic peptides from 0.1 to 5 ug of peptide receptors loaded with peptides and their subsequent sequencing."

The specification further discloses at [0023] that the amount of tissue or bodily fluid necessary to obtain *e.g.* 100 ng of MHC class II molecules depends on the number of cells that do express MHC class II and on the expression rate of MHC class II molecules, e.g., 100 ng of MHC class II are equivalent to about 2 X 10^5 mature DCs or 5 to 10 X10^6 PBM or about 5 X 10^7 PBMC which can be obtained from about 50 ml of blood.

Evidentiary reference Adamshivili *et al* (Rheumatol. Int. 2002, June; 22(2): 71-76) teach that saliva from normal subjects contained levels of soluble HLA class I (s-HLA-I) that were undetectable or ranged from 9 ng/ml to 70 ng/ml, while sHLA-I among 38 patients with moderately active RA or SLE were significantly elevated (especially abstract).

Evidentiary reference Aultman *et al* (Human Immunol. 1999 60(3): 239-244) teach that sHLA-I was nondeductible to low in sweat, saliva and tears from normal subjects, while sHLA-II molecules were found in each of the body fluids tested with considerable variation between individuals (especially abstract).

The evidentiary references establish unpredictability in the art of obtaining sufficient quantities of intact MHC in body fluids other than whole blood.

In contrast, the claims recited that the complexes of MHC must be in an amount of 0.1 to 5ug.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:
    The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-15 and 17-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1, 13, 14 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: separating the antigenic peptides into individual peptides or peptide mixtures, as the claim preamble recites "A method for isolating antigenic peptides in femtomolar amounts of about 16-320 femtomoles", *i.e.,* the recited femtomole amount being that indicative for a single dominant peptide species, as evidenced below. Another omitted step is: testing to determine if the peptides isolated in femtomolar amounts are indeed "antigenic" as the preamble of the claim recites.
The specification at [0029] discloses that each single peptide whose sequence has to be determined is represented in only femtomolar amounts 1 ug MHC class II (16 pmol) may carry dominant peptide species, with each single peptide attaining an occupancy of 0.1-2% which equals about 16-320 femtomoles. The specification continues "The methods of the present invention allow the isolation of these femtomolar amounts of antigenic peptides from 0.1 to 5 ug of peptide receptors loaded with peptides and their subsequent sequencing."

(b) Claims 1, 13 and 14 are indefinite in the recitation of "by sequestering the complexes with immunoprecipitation, wherein the complexes are coupled to beads" because it is not clear what is meant, *i.e.,* if the complexes themselves are coupled to beads or an immunoaffinity reagent is coupled to beads.

(c) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu,* 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 19 recites the broad recitation "body fluids", and the claim also recites "e.g., serum, synovial fluid, ascites" which is the narrower statement of the range/limitation.

(d) Claim 27 contains the trademark/trade name TX-100 (*i.e.,*TRITON-X100). Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35

U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a detergent and, accordingly, the identification/description is indefinite.

`3. For the purpose of prior art rejections, the filing date of the instant claims 6 and 22 is deemed to be the filing date of the instant application, *i.e.,* 10/1/03, as the parent applications do not provide support for the claim limitations "diluted acetonitrile (0.1%), diluted acetic acid (0.1%)".

For the purpose of prior art rejections, the filing date of the instant claims 1-5, 7-15 and 17-21 and 23-27 is deemed to be the filing date of EPO 020222223.8, *i.e.,* 10/2/02.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-3 and 5-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rammensee *et al* (Immunogenetics, 1995, 41: 178-228) in view of van der Heeft *et al* (Anal. Chem. 1998, 70: 3742-3751), Scopes (Protein Purification, 3rd Ed. 1994, Springer-Verlag, NY page 15) and an admission in the specification at [0023].

Rammensee *et al* teach that two classes of MHC are distinguished, class I and class II, both of which bind peptides in their peptide binding grooves. Rammensee *et al* teach that there is a small copy number of individual peptides, *i.e.,* it is estimated that a cell presents well over 1,000 different peptides on its 100,000 or so copies of a given MHC allelic product. "A few of these peptides are present in high copy number, that is, up to 10,000 or more." Rammensee *et al* teach that sequencing by tandem mass spectroscopy has been reported to be sensitive, down to 30 fmol or less. Rammensee *et al* teach providing a source of MHC-expressing cells such as tumor cells, transformed cells, cells transfected to express a specific MHC molecule, or fresh or frozen tissue, followed by detergent extraction, immunoprecipitation of the MHC molecules with solid-phase bound antibodies, dissociation of peptide from MHC molecules with acid such as 0.1% TFA or 10% HAc, ultrafiltration to concentrate the sample, separation of peptides by reversed phase HPLC (RP-HPLC, reversed phase high pressure liquid chromatography) and mass spectrometry (MS) to sequence the peptides. Rammensee *et al* teach human MHC molecules are HLA molecules (especially pages 178-181, Figure 2).

Rammensee *et al* do not teach that the solid-phase that the antibody is attached to is a bead, nor that the cells are dendritic cells, nor that the washing step also comprises ultrafiltration step and is accomplished using water.

van der Heeft *et al* teach a method for detecting low femtomole levels of MHC class I peptides by providing either 5 x 10^9 or 2.75 x 10^9 EBV-transformed B cells expressing HLA-A*0201, detergent lysing said cells with 0.5% Nonidet P40, centrifugation, immunoaffinity purification of the class I MHC molecules by passage of supernatent over a column comprising mAb specific for HLA-A*0201 coupled to Sepharose-4B beads, washing the column, eluting the peptides using 10% HAc, centrifuging through a macroseparation filter, concentration, fractionation by RP-HPLC and sequencing by ISIMS (*i.e.*, a type of mass spectrometry). van der Heeft *et al* teach comparative ligand mapping, *i.e.*, identifying MHC-bound peptides unique to infected cells *vs* uninfected cells, *i.e.*, comparing the peptides identified from cells which have been contacted with a source of potential antigen with those which have been identified from cells which have not been contacted with a source of potential antigen, and wherein the peptides are naturally-processed, and comparison the peptides with the protein(s) that the infected cells were contacted with for identification of the source protein. van der Heeft *et al* teach washing steps and ultrafiltration of the eluted peptides (*i.e.*, centrifugation at 3,000g through a 10kDa macroseparation filter), but is silent as to the identity of the wash solution (see entire reference, especially abstract, page 3741 at columns 1 and 2 of introduction section, Experimental section on page 3744 at column 1, section entitled "Immunoaffinity Purification and Extraction of MHC-Associated Peptides", section spanning pages 3744-3745, Figure 4 legend, second paragraph at column 2 on page 3750).

Scopes teaches that ultrafiltration of protein solutions removes water and small molecules, leaving a more concentrated protein solution behind (page 15).

The admission in the specification at [0023] is that the amount of tissue or bodily fluid necessary to obtain *e.g.* 100 ng of MHC class II molecules depends on the number of cells that do express MHC class II and on the expression rate of MHC class II molecules, e.g., 100 ng of MHC class II are equivalent to about 2 X 10^5 mature DCs or 5 to 10 X10^6 PBM or about 5 X 10^7 PBMC which can be obtained from about 50 ml of blood.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an antibody attached to a bead as taught by van der Heeft *et al*, and to wash the sequestered complexes as taught by Van der Heeft et al with water or PBS using ultrafiltration such as taught by Scopes.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Rammensee *et al* do not teach what the solid phase is, but

van der Heeft *et al* do provide this teaching in the form of a bead to which the antibody may be coupled. As pertains to a washing step via ultrafiltration, one of ordinary skill in the art at the time the invention was made would have been motivated to do this because both Rammensee *et al* and van der Heeft *et al* teach ultrafiltration and the routineer was aware that ultrafiltration could be used to wash as well as to concentrate small samples of proteins or peptides because of the nature of the technique, *i.e.,* the membrane would allow wash buffers or water to flow through the membrane, while the protein or peptides are retained. Scopes teaches that proteins may be subjected to ultrafiltration to concentrate them, and so one of ordinary skill would have been motivated to wash the complexes with water using ultrafiltration, not only to wash the complexes, but to concentrate the solution prior to elution of the peptides so that an appropriately small volume might be applied to the RP-HPLC column.

With regard to the limitation of "A method for isolating antigenic peptides in amounts of about 16 to 32 femtomoles", both references teach methods for isolating peptides in low femtomole amounts, and Rammensee *et al* teaches 30 fmol or less.

With regard to the limitation "in an amount of 0.1 to 5 ug", although Rammensee *et al* is silent as to this limitation, van der Heeft *et al* teach that the number of cells used is either 5×10^9 or 2.75×10^9 EBV-transformed B cells expressing HLA-A*0201. Given the admission in the specification at [0023] about the equivalence of the number of cells to the amount of MHC complex, the claimed process appears to be the same or similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

16. Claims 4 and 14-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rammensee *et al* (Immunogenetics, 1995, 41: 178-228) in view of van der Heeft *et al* (Anal. Chem. 1998, 70: 3742-3751)), Scopes (Protein Purification, 3rd Ed. 1994, Springer-Verlag, NY page 15) and an admission in the specification at [0023] as applied to claims 1-3 and 5-13 above, and further in view of Arndt *et al* (The EMBO Journal, 2000, 19(6): 1241-1251, IDS reference).

The combination of Rammensee *et al* (Immunogenetics, 1995, 41: 178-228) in view of van der Heeft *et al, Scopes* and an admission in the specification at [0023] has been discussed supra.

The said combination does not teach wherein the cells isolated from a mammal are dendritic cells, nor wherein the dendritic cells (or other class II expressing cells) are first provided and then contacted with a source of potential antigen, nor wherein the cells are exposed to a potential source of antigens as immature DC at the same time as they are induced to mature to dendritic cells.

Arndt *et al* teach immunopurification of peptide-containing MHC class II complexes from B cells and immature dendritic cells (DC), as well as a similarity of antigen loading and presentation by the two antigen presenting cell (APC) types. Arndt *et al* teach that B cells and DC can load antigenic peptides either on newly synthesized class II molecules in lysosome-like organelles named MIICs, or on recycling class II molecules in early endosomes and on the cell surface. Arndt *et al* teach maturation of dendritic cells using TNF-α over a period of about three days, and that upon such cytokine-induced maturation, DC were revealed to down-regulate their surface DM and concomitantly lose the ability to load peptide. Arndt *et al* teach exogenous antigenic peptide loading or administration of exogenous protein antigen. Arndt *et al* teach antigenic peptides from influenza virus HA protein and from MBP autoantigen (see entire reference, especially abstract, paragraph spanning pages 1231-1242, Figure 1 legend, Figure 6 legend, paragraph spanning columns 1-2 on page 1246, paragraph spanning columns 1-2 on page 1248, and last paragraph of reference on page 1248, materials and methods section).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used dendritic cells in the method of the combined references in place of B cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Arndt *et al* teach that both B cells and DC are APC that load and present antigenic peptides in a similar manner.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have contacted the DC with a potential source of antigen, as is taught by Arndt *et al*.
One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study the peptides that could be naturally processed and loaded onto class II MHC molecules or to assess the ability of peptides to bind to a particular MHC class II molecule.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have contacted the DC with a potential source of antigen at the same time as contacting the DC with TNF-α to induce maturation.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to take advantage of the DC ability to load antigenic peptides while immature, as Arndt *et al* provide such teaching regarding the ability of immature *vs* mature DC to load antigen.

Claim 15 is included in this rejection because dendritic cells and B cells express both class I and class II MHC molecules.

17. Claims 4 and 14-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rammensee *et al* (Immunogenetics, 1995, 41: 178-228) in view of van der Heeft *et al* (Anal. Chem. 1998, 70: 3742-3751) and an admission in the specification at [0023] as applied to claims 1-3 and 5-13 above, and further in view of Arndt *et al* (The EMBO Journal, 2000, 19(6): 1241-1251, IDS reference) and Kropshofer *et al* (Nature, 1/02, 3(1): 61-68).

The combination of Rammensee *et al* (Immunogenetics, 1995, 41: 178-228) in view of van der Heeft *et al* and an admission in the specification at [0023] has been discussed supra.

The said combination does not teach wherein the cells isolated from a mammal are dendritic cells, nor wherein the dendritic cells (or other class II expressing cells) are first provided and then contacted with a source of potential antigen, nor wherein the cells are exposed to a potential source of antigens as immature DC at the same time as they are induced to mature to dendritic cells, nor wherein the cells are solubilized with the detergent TRITON-X100.

Arndt *et al* teach immunopurification of peptide-containing MHC class II complexes from B cells and immature dendritic cells (DC), as well as a similarity of antigen loading and presentation by the two antigen presenting cell (APC) types. Arndt *et al* teach that B cells and DC can load antigenic peptides either on newly synthesized class II molecules in lysosome-like organelles named MIICs, or on recycling class II molecules in early endosomes and on the cell surface. Arndt *et al* teach maturation of dendritic cells using TNF-α over a period of about three days, and that upon such cytokine-induced maturation, DC were revealed to down-regulate their surface DM and concomitantly lose the ability to load peptide. Arndt *et al* teach exogenous antigenic peptide loading or administration of exogenous protein antigen. Arndt *et al* teach antigenic peptides from influenza virus HA protein and from MBP autoantigen (see entire reference, especially abstract, paragraph spanning pages 1231-1242, Figure 1 legend, Figure 6 legend, paragraph spanning columns 1-2 on page 1246, paragraph spanning columns 1-2 on page 1248, and last paragraph of reference on page 1248, materials and methods section).

The combination of Rammensee *et al* (Immunogenetics, 1995, 41: 178-228) in view of van der Heeft *et al* and an admission in the specification at [0023] has been discussed supra.

The said combination does not teach wherein the cells isolated from a mammal are dendritic cells, nor wherein the dendritic cells (or other class II expressing cells) are first provided and then contacted with a source of potential antigen, nor wherein the cells are exposed to a potential source of antigens as immature DC at the same time as they are induced to mature to dendritic cells, nor that TX-100 is used to solubilize the cells.

Arndt *et al* teach immunopurification of peptide-containing MHC class II complexes from B cells and immature dendritic cells (DC), as well as a similarity of antigen loading and presentation by the two antigen presenting cell (APC) types. Arndt *et al* teach that B cells and DC can load antigenic peptides either on newly synthesized class II molecules in lysosome-like organelles named MIICs, or on recycling class II molecules in early endosomes and on the cell surface. Arndt *et al* teach maturation of dendritic cells using TNF-α over a period of about three days, and that upon such cytokine-induced maturation, DC were revealed to down-regulate their surface DM and concomitantly lose the ability to load peptide. Arndt *et al* teach exogenous antigenic peptide loading or administration of exogenous protein antigen. Arndt *et al* teach antigenic peptides from influenza virus HA protein and from MBP autoantigen (see entire reference, especially abstract, paragraph spanning pages 1231-1242, Figure 1 legend, Figure 6 legend, paragraph spanning columns 1-2 on page 1246, paragraph spanning columns 1-2 on page 1248, and last paragraph of reference on page 1248, materials and methods section).

Kropshofer *et al* teach solubilizing cells expressing class II MHC in TX-100 (TRITON-X100) as a preliminary step in isolating class II MHC molecules (especially materials and methods on page 67 at column 2 at the 6th full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used dendritic cells in the method of the combined references in place of B cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Arndt *et al* teach that both B cells and DC are APC that load and present antigenic peptides in a similar manner.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have contacted the DC with a potential source of antigen, as is taught by Arndt *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to study the peptides that could be naturally processed and

loaded onto class II MHC molecules or to assess the ability of peptides to bind to a particular MHC class II molecule.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have contacted the DC with a potential source of antigen at the same time as contacting the DC with TNF-α to induce maturation.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to take advantage of the DC ability to load antigenic peptides while immature, as Arndt *et al* provide such teaching regarding the ability of immature *vs* mature DC to load antigen.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any suitable detergent for solubilizing cells, such as TX-100 taught by Kropshofer *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to isolate MHC class II molecules as taught by the combined references.

Claim 15 is included in this rejection because dendritic cells and B cells express both class I and class II MHC molecules.

18. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 recites that the provided peptide receptors comprise MHC II molecules, and base claim 1 also recites the complexes provided are MHC class II peptide receptors.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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